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Interventional Cardiology

Preventive effects of an antiallergic drug, pemirolast potassium, on restenosis after percutaneous transluminal coronary angioplasty

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Background We recently confirmed that pemirolast potassium, an antiallergic agent, markedly inhibits migration and proliferation of vascular smooth muscle cells. It has also been reported that pemirolast inhibits intimal hyperplasia in animal experiments.

Methods and Results To elucidate the preventive effects of pemirolast on restenosis after percutaneous transluminal coronary angioplasty (PTCA), 227 patients were enrolled in this prospective, randomized trial. A total of 205 patients who were compatible with the protocol were analyzed (pemirolast group, 104 patients with 140 lesions; control group, 101 patients with 133 lesions). Patients in the pemirolast group received 20 mg/d of pemirolast from 1 week before PTCA until the time of follow-up angiography (4 months after PTCA). Angiographic restenosis was defined as diameter stenosis ≥50% at follow-up. Restenosis rates were significantly lower in the pemirolast group than in the control group (24.0% vs 46.5% of patients, 18.6% vs 35.3% of lesions, $P < .01$, respectively). During 8 months of follow-up, there were no coronary events (death, myocardial infarction, coronary artery bypass surgery, or repeated PTCA) in 81.7% of the pemirolast group and in 63.4% of the control group ($P = .013$).

Conclusions This study suggested that pemirolast would be useful in the clinical setting to prevent restenosis after PTCA. (Am Heart J 1998;136:1081-7.)

Restenosis after percutaneous transluminal coronary angioplasty (PTCA) remains an important unsolved problem. Stenting has contributed to reduction of restenosis by preventing pathologic vascular remodeling,[1,2] but the proliferation of vascular smooth muscle cells (VSMC), one of the causes of restenosis, is observed even after stent placement.[3] Pharmacologic strategies that prevent the proliferation of VSMC in animals have been ineffective in human beings. Recently, the antiallergic and antikeloid drug tranilast was reported to be effective in preventing restenosis after PTCA[4,5] in Japan. Experimental studies have shown that tranilast particularly inhibits collagen synthesis[6] through the suppression of transforming growth factor (TGF)-β1,[7] which suggests that tranilast may prevent restenosis. On the other hand, we recently confirmed that pemirolast potassium,[8-12] an antiallergic agent widely used in Japan, markedly inhibits migration and proliferation of VSMC, mainly by inhibition of inositol phospholipid turnover, which is the initial stage of the intracellular signal transduction system.[13] The inhibitory effects of pemirolast on VSMC proliferation are found to be higher than those of tranilast (unpublished data).

Furthermore, it has been reported that pemirolast inhibits intimal hyperplasia in animal experiments.[14] On the basis of these results, we conducted a clinical prospective, randomized study to investigate the preventive effects of pemirolast on restenosis after PTCA.

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Methods

Patient selection

The study population consisted of patients with symptomatic ischemic heart disease caused by de novo lesions of the native coronary artery. The specific angiographic criterion for enrollment was ≥75% stenosis to be dilated (classification of

percentage of stenosis by the American Heart Association Committee Report[15]). The criteria for exclusion were acute myocardial infarction, left ventricular ejection fraction of ≤40%, and renal failure treated with hemodialysis. The angiographic criteria for exclusion were the presence of type C lesions[16] such as chronic total occlusion (≥3 months old), ostial lesions, diffuse lesions, and left main trunk lesions.

After the patients were interviewed to determine their eligibility and had been given informed consent, they were randomly and prospectively assigned to one of two groups: a group given pemirolast (pemirolast group) or a group not given pemirolast (control group).

Drug treatments

The pemirolast group was given 20 mg/d pemirolast, its standard dose as an antiallergic drug, from 1 week before PTCA until follow-up angiography 4 months later. All subjects in both groups were given aspirin (81 mg/d), nitrate, calcium antagonists, and/or β-blockers (selected at the discretion of attending physicians) from at least 1 week before the procedure to follow-up angiography 4 months later. Drugs for treating complications such as hypertension, hyperlipidemia, and diabetes mellitus were used at the discretion of attending physicians, but the use of other antiallergic drugs was prohibited.

Angioplasty protocol

Angioplasty was performed with the conventional techniques. Immediately before the procedure, patients received an initial bolus injection of heparin (8000 to 10,000 units) and intracoronary administration of 200 μg nitroglycerin. By using balloon angioplasty, investigators attempted to achieve an optimal result, which was defined as residual stenosis of <30% of the luminal diameter according to a visual estimate, without any complications (death, myocardial infarction, coronary artery bypass surgery [CABG], or bail-out stenting). Heparin and nitroglycerin infusions were continued for 24 hours after the procedure.

Follow-up

All treated patients were monitored for at least 8 months. Adverse effects attributable to pemirolast were monitored at the fixed periods (before administration and 1 day, 2 weeks, and 4 months after PTCA) by interview as well as by laboratory examinations. Coronary angiography was repeated 4 months after PTCA. If ischemic symptoms recurred within 4 months after PTCA, coronary angiography was performed earlier. If no definite restenosis was found, a subsequent angiography was repeated 4 months later.

Angiographic analysis

Coronary angiograms obtained before, immediately after, and 4 months after PTCA were reviewed by an unbiased angiographer without knowledge of group randomization. All views were recorded after intracoronary administration of nitroglycerin (200 μg). Lesions were visualized in multiple views and scored according to the presence of eccentricity, irregularity, calcification, thrombus, ulceration, and so on.

For quantitative analysis, end-diastolic cineframes were selected from the angiographic views demonstrating the maximal degree of stenosis and were matched before, immediately after, and at follow-up. The selected cineframes were digitalized with a cinevideo converter, and a computer edge-detection algorithm was applied to the arterial and catheter contours (Coronary analyzer system; PADL Co, Osaka, Japan). With the guiding and diagnostic catheters as the calibration standard, reference diameter, minimal lumen diameter, and percentage of diameter stenosis were calculated. Acute gain was defined as the increase in minimal lumen diameter immediately after PTCA, late loss as the decrease in minimal lumen diameter at follow-up (postprocedure minus follow-up minimal lumen diameter), and net gain as the difference between acute gain and late loss. Successful angioplasty was defined as the reduction of diameter stenosis to <50%. Angiographic restenosis was defined as a diameter stenosis ≥50% at the end of follow-up.

End points

The primary end point of the trial was angiographic evidence of restenosis at follow-up. Secondary end points were clinical: occurrence of acute closure, acute myocardial infarction, repeated PTCA, and CABG within the first 8 months after the initial PTCA. Event-free survival was defined as absence of death, myocardial infarction, or repeated revascularization by PTCA or CABG.

Statistical analysis

For the analysis of continuous variables, the Student's *t* test was used to assess differences between the pemirolast group and the control group. The results are expressed as mean ± SD. Categorical variables, which are presented as rates, were compared by chi-square test, except for the composite clinical end point and revascularization of the target lesion, which were analyzed by means of Kaplan-Meier survival curves, with differences between the 2 groups compared by Wilcoxon test. Statistical significance was defined as $P < .05$.

Results

Between January 1994 and June 1996, 227 patients were enrolled in this study. Twenty-two of them were excluded from evaluation because of the failure or suboptimal results of PTCA (17 patients), deviation from the protocol (2 patients), or lack of follow-up angiography (3 patients). Thus the final study group comprised 205 patients, with 104 patients (140 lesions)

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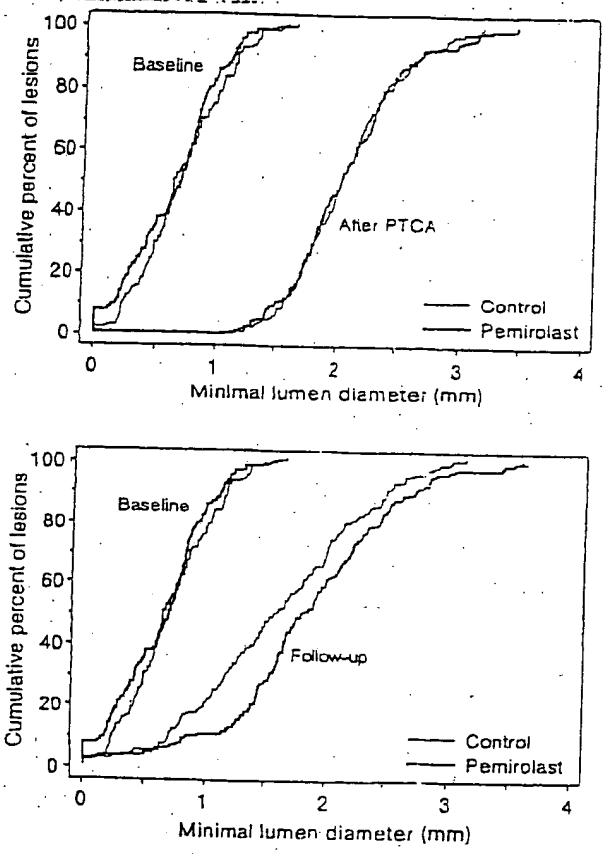
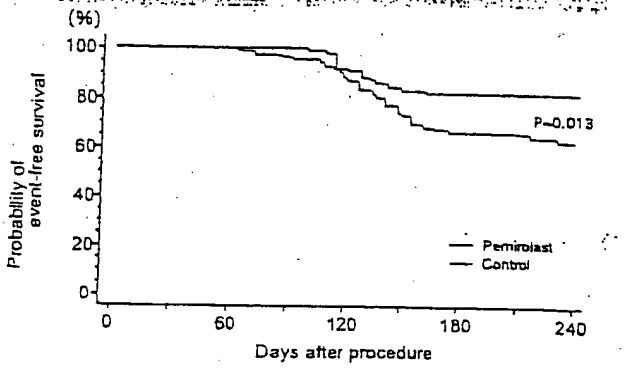
Figure 1



Cumulative frequency distribution curves.

Figure 2



Kaplan-Meier survival curves for major cardiac events (death, myocardial infarction, coronary artery bypass surgery, and repeated angioplasty).

in the pemirolast group and 101 patients (133 lesions) in the control group.

Baseline characteristics

Baseline clinical characteristics are shown in Table I, and baseline angiographic and procedure-related characteristics are shown in Table II. There were no significant differences in baseline characteristics between the 2 groups except for a higher incidence of chronic occluded lesions (<3 months old) in the pemirolast group than in the control group.

Angiographic results

The average time to follow-up angiography was 4.2 ± 0.7 months (pemirolast group: 4.0 ± 0.4 months; control group: 4.4 ± 0.8 months, not significant [NS]). Luminal dimensions at baseline, immediately after PTCA, and at follow-up are shown in Table III. At baseline, there were no differences between the 2 groups in reference diameter, minimal lumen diameter, or severity of stenosis. Immediately after PTCA, there were no differences in minimal lumen diameter, severity of stenosis, or acute gain between the 2 groups, whereas at follow-up the pemirolast group had a smaller mean reduction in minimal lumen diameter (late loss: 0.20 ± 0.61 vs 0.46 ± 0.57 mm, $P < .001$) and larger net gain (1.23 ± 0.68 vs 0.91 ± 0.62 mm, $P < .001$), resulting in a larger minimal lumen diameter (1.87 ± 0.70 vs 1.62 ± 0.68 mm, $P < .001$) and a lower severity of stenosis (33.6% ± 20.9% vs 43.6% ± 19.5%, $P < .001$). The cumulative distribution of the minimal lumen diameter is shown in Fig 1. Restenosis rates both per lesion and per patient in the pemirolast group were lower than those in the control group (18.6% vs 35.3% and 24.0% vs 46.5%, $P = .002$, respectively).

Clinical outcomes

The numbers of various types of clinical events at 8 months among all 205 patients are shown in Table IV. During follow-up no patient died in either group, but 1 patient in the control group had a non-Q-wave myocardial infarction caused by restenosis and received elective CABG. The incidence of recurrent angina was significantly lower in the pemirolast group than in the control group (6.7% vs 19.8%, $P = .012$). There was no significant difference in the incidence of a positive treadmill test between the pemirolast group and the control group (11.5% vs 16.8%). A repeated angioplasty was performed on

Table I. Baseline clinical characteristics

	Pemirolast (n = 104)	Control (n = 101)	P value
Male sex	78.8	75.2	NS
Age (mean ± SD years)	62 ± 10	61 ± 10	NS
Unstable angina	38.5	26.7	NS
History of myocardial infarction	41.3	39.6	NS
Hyperlipidemia	51.9	46.5	NS
Hypertension	52.9	40.6	NS
Current smoker	41.3	35.6	NS
Obesity (body mass index ≥26)	29.8	30.7	NS
Diabetes mellitus	28.8	26.7	NS
Hyperuricemia	12.5	13.9	NS
Concomitant drugs			
Nitrates	88.5	85.1	NS
Antiplatelet agent (aspirin, 81 mg)	94.2	97.0	NS
Calcium channel blockers	76.0	72.3	NS
β-Blockers	46.2	50.5	NS
ACE inhibitors	20.2	15.8	NS
Antilipemic drugs (pravastatin or simvastatin)	26.9	20.8	NS
No. of target lesions per patient			NS
1	62.5	63.4	
2	22.1	29.7	
3	15.4	6.9	

Values are % of patients.

those patients who showed such ischemic signs. The incidence of repeat angioplasty was lower in the pemirolast group than in the control group (18.3% vs 36.6%, P = .005). In addition, 6 patients (5.8%) in the pemirolast group and 9 control patients (8.9%) in whom ischemic signs were not recognized were followed up medically. The results demonstrated that the event-free survival rate was significantly higher in the pemirolast group than in the control group (81.7% vs 63.4%, P = .013) (Fig 2).

A slight elevation of glutamic-pyruvic transaminase was observed in 1.9% (2 of 104) of patients 1 to 2 weeks after starting administration of pemirolast, but this returned to the baseline level after 2 weeks without interruption of administration. One of the 2 patients was positive for hepatitis C virus antibody. Neither symptoms nor significant aggravation of laboratory findings attributable to pemirolast were observed in the other 102 patients.

Discussion

Before our study, Kato et al[5] noted the similarity of reparative processes of vascular wall injury, VSMC proliferation, and extracellular matrix synthesis to the process of keloid formation and conducted multicenter, placebo-controlled, double-blind studies to elucidate the preventive effects of the antiallergic and antikeloid drug tranilast on restenosis after PTCA.[4,5] They reported that tranilast reduced clinical restenosis at 3 months after PTCA.[4]

In the current randomized comparative study, the antiallergic agent pemirolast was found to reduce not only the angiographic restenosis rate but also late cardiac events. Pemirolast is known to result in minor and infrequent adverse events in 3.6% of 112 patients (nausea: 0.9%, headache: 0.9%, exanthema: 0.9%, slight increase in number of platelets: 0.9%) in comparison with tranilast (12.4% of 113 patients).[12] A low incidence of adverse effects (1.9%) was confirmed in the current study. These results suggest that pemirolast has pharmacologic properties useful in preventing restenosis after PTCA.

However, the exact mechanisms are not known. The results of preclinical studies both in vitro[13] and in vivo[14] suggest that pemirolast reduces restenosis by preventing neointimal hyperplasia. In recent years, serial (after angioplasty and follow-up) intravascular ultrasound (IVUS) studies[17,18] have been performed to examine the restenosis process after PTCA, and it has been determined that 2 basic underlying mechanisms, namely neointimal proliferation and vascular remodeling, participate in restenosis. Further, it has been considered that neointimal hyperplasia is solely responsible for in-stent restenosis.[3,18] Our serial IVUS study in

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Table II. Angiographic and procedure-related characteristics

	% of Lesions		
	pemirolast (n = 140)	control (n = 133)	P value
Target vessel			
Left anterior descending	44.3	45.9	NS
Left circumflex	28.5	27.8	NS
Right coronary artery	27.9	26.3	NS
With collaterals	18.6	17.3	NS
Infarct-related lesion	25.7	23.3	NS
Type of lesion			NS
Type A	26.4	30.1	
Type B	73.6	69.9	
Lesion morphology			
Concentric	28.6	32.3	NS
Eccentric	37.1	38.3	NS
Major branch involved	10.0	11.3	NS
Irregular contour	15.7	12.8	NS
Calcified	10.0	9.8	NS
Occluded (<3 months old)	11.4	4.5	.04
Thrombus	4.3	2.3	NS
Ulceration	5.7	4.5	NS
Dissection	2.1	1.5	NS
Lesion length (mm)	6.9 ± 3.4	6.5 ± 3.3	NS
Balloon/artery ratio	1.14 ± 0.18	1.14 ± 0.15	NS
Inflation of the largest balloon			
Frequency	3.1 ± 1.3	3.0 ± 1.2	NS
Maximal pressure (atm)	9.5 ± 2.1	9.5 ± 2.5	NS
Total inflation time (s)	213 ± 128	200 ± 86	NS

patients treated with balloon angioplasty documented that pemirolast does not prevent vascular remodeling but does prevent neointimal hyperplasia. Furthermore, a similar study in patients with stent placements supported the view that the inhibitory action of pemirolast on neointimal hyperplasia is responsible for restenosis prevention (unpublished data). Consequently, it is considered that concomitant therapy by stenting and with pemirolast is more useful for preventing restenosis.

VSMC proliferation and the production of extracellular matrix are the result of complex processes[19-21] involving cytokines such as growth factors, arachidonic acid metabolites, and endothelium-derived contraction factors. Consequently, inhibition of the intracellular signal transduction systems common to many cytokines is likely to result in the effective inhibition of VSMC proliferation. Up to now, 2 pathways for these intracellular signal transduction proliferation systems are known,[22] one of which involves membrane inositol phospholipid turnover[23] starting from the activation of receptor tyrosine kinase. We confirmed through molecular biologic testing that pemirolast markedly inhibits VSMC proliferation induced by platelet-derived growth factor, angiotensin II, or endothelin 1. In addition, we found that pemirolast suppresses membrane inositol phospholipid turnover at an early stage of the intracellular signal transduction system, which suggests that this is one of the mechanisms by which the agent inhibits VSMC proliferation.[13] It has been reported that tranilast prevents VSMC proliferation and collagen synthesis through the suppression of TGF-β1.[6,7] However, it remains to be elucidated whether pemirolast also acts through the suppression of TGF-β1.

The first steps have just been taken toward elucidating the mechanisms by which tranilast and pemirolast inhibit restenosis and clarifying the exact mechanisms of their actions. The common pharmacologic characteristics of tranilast and pemirolast as antiallergic agents is that both compounds have activity in targeting mast cells. It is well known that mast cells exist abundantly in the vascular wall, especially in the adventitia, and that they secrete chymase, an angiotensin II–forming enzyme.[24-26]

Experimental studies have shown that angiotensin II promotes the proliferation of VSMC and extracellular

Table III. Angiographic analysis

	Pemirolast (n = 140)	Control (n = 133)	P value
Before the procedure			
Reference diameter (mm)	2.70 ± 0.56	2.70 ± 0.53	NS
Minimal lumen diameter (mm)	0.63 ± 0.35	0.71 ± 0.34	NS
Stenosis (%)	76.4 ± 11.9	74.7 ± 10.6	NS
After the procedure			
Minimal lumen diameter (mm)	2.07 ± 0.46	2.07 ± 0.42	NS
Stenosis (%)	21.4 ± 8.9	22.1 ± 8.9	NS
At follow-up			
Minimal lumen diameter (mm)	1.87 ± 0.70	1.62 ± 0.68	.003
Stenosis (%)	33.6 ± 20.9	43.6 ± 19.5	<.001
Change in minimal lumen diameter			
Acute gain (mm)	1.44 ± 0.52	1.37 ± 0.43	NS
Late loss (mm)	0.20 ± 0.61	0.46 ± 0.57	<.001
Net gain (mm)	1.23 ± 0.68	0.91 ± 0.62	<.001
Restenosis			
Lesions (%)	26/140 (18.6)	47/133 (35.3)	.002
Patients (%)	25/104 (24.0)	47/101 (46.5)	.002

Table IV. Cardiac events caused by restenosis during 8-month follow-up

	Pemirolast (n = 104)	Control (n = 101)	P value
Cardiac death	0	0	
Myocardial infarction	0	1 (1.0 %)	
Recurrent angina	7 (6.7%)	20 (19.8%)	.012
Electrocardiographic changes during exercise	12 (11.5%)	17 (16.8%)	
Neither angina nor electrocardiographic changes	6 (5.8%)	9 (8.9%)	
Repeated angioplasty	19 (18.3%)	36 (35.6%)	.005
Elective CABG	0	1 (1.0%)	

matrix by activating platelet-derived growth factor, TGF-β, basic fibroblast growth factor, and endothelin 1.[27,28] Injury to the intima of the carotid artery in dogs has been shown to lead to an increase in the number of mast cells in the adventitia and fibrotic outgrowth as well as intimal hyperplasia. Moreover, an increase in angiotensin II levels and a chymase level exceeding the angiotensin-converting enzyme (ACE) level were demonstrated in the injured vascular wall.[26]

Given these reports, it is important to examine the effects of pemirolast on the chymase-dependent angiotensin II–forming pathway, and we will perform further studies to elucidate the mechanisms by which pemirolast prevents restenosis

Limitations

Because this study was not a double-blind but an open study, a double-blind study must still be done. The most appropriate time to begin administration is an important issue to be determined. If VSMC proliferation begins in the first 24 hours after PTCA, as has been reported,[29] preprocedural administration is likely to be more effective. In this study, therefore, administration was started 1 week before PTCA. If efficacy is not affected, however, it would be sensible and desirable to begin administration after the procedure. Further studies are required to determine the ideal dosage, appropriate time to begin administration, and duration of administration to bring pemirolast into clinical use as a new preventive modality of restenosis.

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